

1322

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A61K 38/21</b>		<b>A1</b>	(11) International Publication Number: <b>WO 98/33517</b> (43) International Publication Date: 6 August 1998 (06.08.98)
(21) International Application Number: PCT/GB98/00269 (22) International Filing Date: 29 January 1998 (29.01.98) (30) Priority Data: 9702021.8 31 January 1997 (31.01.97) GB (71) Applicant (for all designated States except US): IMPERIAL COLLEGE OF SCIENCE, TECHNOLOGY & MEDICINE [GB/GB]; Sherfield Building, Imperial College, London SW7 2AZ (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): FOSTER, Graham, Russell [GB/GB]; The Imperial School of Medicine, Dept. of Medicine, Queen Elizabeth The Queen Mother Wing, St. Mary's Hospital, London W2 1PG (GB). THOMAS, Howard, Christopher [GB/GB]; The Imperial School of Medicine, Dept. of Medicine, Queen Elizabeth The Queen Mother Wing, St. Mary's Hospital, London W2 1PG (GB). (74) Agents: CHAPMAN, Paul, William; Kilburn & Strode, 20 Red Lion Street, London WC1R 4PJ (GB) et al.		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: USE OF INTERFERON ALPHA SUBTYPES FOR ENHANCING IMMUNE RESPONSE			
(57) Abstract  The use of an IFN- $\alpha$ subtype is provided for the preparation of a medicament to enhance the T-cell immune response in therapy of cancer, bacterial or parasitic infection or systemic viral infection amongst other disease conditions. Also provided are pharmaceutical formulations which include such sub-types of IFN- $\alpha$ and methods of treatment, including treatment of cancer, bacterial or parasitic infection or systemic viral infection amongst other disease conditions.			

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

## USE OF INTERFERON ALPHA SUBTYPES FOR ENHANCING IMMUNE RESPONSE

The present invention relates to the use of Interferon- $\alpha$  (IFN- $\alpha$ ) subtypes, particularly IFN- $\alpha_3$ , in the preparation of medicaments to treat certain diseases as well as methods of immunomodulation comprising administration of one or more IFN- $\alpha$  subtypes.

Type I interferons (IFN) are a family of closely related glycoproteins containing many IFN- $\alpha$  subtypes and one IFN- $\beta$  subspecies. At least 13 different human IFN- $\alpha$  subtypes have been identified by analysis of human cDNA libraries and by protein analysis of the IFNs produced by stimulated lymphoblastoid cells. The reasons for this heterogeneity are not yet known. Previous studies have suggested that all Type I IFNs bind to an identical receptor and therefore have identical effects. However a mutant cell line that responds only to IFN- $\beta$  and interferon- $\alpha_3$  but not other IFN- $\alpha$  subtypes has been identified showing that these two IFN subspecies either bind to a different receptor or bind in a different way and may therefore have different effects. Molecular analysis of the human Type I IFN receptor thus suggests that the receptor may be able to distinguish between different IFN subtypes.

20

A number of studies have compared the effects of different IFN- $\alpha$  subtypes on the antiviral activities of human cell lines. Zoon *et al* (J. Biol. Chem. 267:15210-

16 (1992) studied IFNs that were obtained from HPLC purification of natural IFN and found no gross differences in their antiviral activities. However, Sperber *et al*, J. Interferon. Res. 12 363-368 (1992) examined the effects of different recombinant IFN- $\alpha$  subtypes on cells infected with the human immunodeficiency virus (HIV) and found marked differences in their antiviral properties. WO95/24212 disclosed that different IFN- $\alpha$  subtypes were effective antiviral agents in different cell types.

25

Thus, it is possible to target viral infections in say the liver by the use of particular subtypes, eg IFN- $\alpha_8$ .

5 B cells or B lymphocytes are a subset of lymphocytes found in secondary lymphoid organs as well as circulating in the blood. They are characterised by the possession of antigen-specific cell surface immunoglobulin molecules of a single antigen-binding specificity which act as receptors for antigen. The interaction of antigen with the cell-surface immunoglobulin is in part responsible for subsequent proliferation of the B cells and their development into antibody-secreting plasma  
10 cells. We have found that B cell proliferation can be induced by certain IFN- $\alpha$  subtypes.

T cells are a class of lymphocytes which mediate immune recognition and effect cell-mediated immune responses. In the course of a normal immune response, the  
15 binding of a ligand (normally the antigenic complex of peptide and MHC molecule) to the T cell receptor complex (TCR-CD3) on the surface of a T cell initiates intracellular changes, usually leading to proliferation of the T cell concerned and the production of lymphokines.

20 We have now found that IFN- $\alpha$  subtypes are capable of manipulating the T cell response and particularly enhancing the T cell immune response.

Thus, in a first aspect the present invention provides the use of an IFN- $\alpha$  subtype in the preparation of a medicament to enhance the T cell immune response. In  
25 particular, IFN- $\alpha_8$  is used.

In view of the ability of IFN- $\alpha$  subtypes to enhance the T cell immune response it is possible to use them in the preparation of medicaments to treat certain disease states. Thus, in further aspects the present invention provides:

i) the use of an IFN- $\alpha$  subtype in the preparation of a medicament for the treatment of cancer;

5 ii) the use of an IFN- $\alpha$  subtype in the preparation of a medicament for the treatment of a bacterial or parasitic infection; and

iii) the use of an IFN- $\alpha$  subtype in the preparation of a medicament to treat a systemic viral infection.

10

Although WO95/24212 disclosed the use of certain IFN- $\alpha$  subtypes in the treatment of viral infections in certain cell types, the present invention relates to their use to treat viral infections which are effectively "systemic", ie viral infections which affect more than one cell or tissue type.

15

Methods for the treatment of the above-noted conditions are also included within the scope of the present invention. Such methods will comprise administration of an effective amount of an IFN- $\alpha$  subtype, in particular IFN- $\alpha_8$ , to the subject.

20 In yet further aspects the present invention provides:

i) a pharmaceutical formulation for use in enhancing the T cell immune response which comprises an IFN- $\alpha$  subtype, optionally together with one or more pharmaceutically acceptable carriers, excipients or diluents;

25

ii) a pharmaceutical formulation for use in the treatment of cancer which comprises an IFN- $\alpha$  subtype, optionally together with one or more pharmaceutically acceptable carriers, excipients or diluents;

5           iii) a pharmaceutical formulation for use in the treatment of bacterial or parasitic infections which comprises an IFN- $\alpha$  subtype, optionally together with one or more pharmaceutically acceptable carriers, excipients or diluents; and

10           iv) a pharmaceutical formulation for use in the treatment of systemic viral infections which comprises an IFN- $\alpha$  subtype, optionally together with one or more pharmaceutically acceptable carriers, excipients or diluents.

In all the above cases the preferred IFN- $\alpha$  subtype is IFN- $\alpha_8$ .

15           Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per dose. The precise dose will of course depend on the condition being treated, the route of administration and the age, weight and condition of the patient.

20           Pharmaceutical compositions within the scope of the present invention may include one or more of the following; preserving agents, solubilising agents, stabilising agents, wetting agents, emulsifiers, sweeteners, colorants, odourants, salts, buffers, coating agents or antioxidants. They may also contain therapeutically active agents.

25           Pharmaceutical compositions within the scope of the present invention may be adapted for a administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such a composition may be

prepared by any method known in the art of pharmacy, for example by admixing the active ingredient with a carrier under sterile conditions.

Various routes of administration will now be considered in greater detail:

5

*(I) Oral Administration*

Pharmaceutical compositions adapted for oral administration may be provided as capsules or tablets; as powders or granules; as solutions, syrups or suspensions (in aqueous or non-aqueous liquids); as edible foams or whips; or as emulsions.

10

Tablets or hard gelatine capsules may comprise lactose, maize starch or derivatives thereof, stearic acid or salts thereof.

Soft gelatine capsules may comprise vegetable oils, waxes, fats, semi-solid, or liquid polyols etc.

15

Solutions and syrups may comprise water, polyols and sugars. For the preparation of suspensions oils (e.g. vegetable oils) may be used to provide oil-in-water or water-in-oil suspensions.

20

*(ii) Transdermal Administration*

Pharmaceutical compositions adapted for transdermal administration may be provided as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis (iontophoresis is described in *Pharmaceutical Research*, 3(6):318 (1986)).

25

*(iii) Topical Administration*

Pharmaceutical compositions adapted for topical administration may be provided

as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For infections of the eye or other external tissues, for example mouth and skin, a  
5 topical ointment or cream is preferably used. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water base or a water-in-oil base.

Pharmaceutical compositions adapted for topical administration to the eye include  
10 eye drops. Here the active ingredient can be dissolved or suspended in a suitable carrier, e.g. in an aqueous solvent.

Pharmaceutical compositions adapted for topical administration in the mouth include lozenges, pastilles and mouthwashes.

15

*(iv) Rectal Administration*

Pharmaceutical compositions adapted for rectal administration may be provided as suppositories or enemas.

20 *(v) Nasal Administration*

Pharmaceutical compositions adapted for nasal administration which use solid carriers include a coarse powder (e.g. having a particle size in the range of 20 to 500 microns). This can be administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nose from a container of powder held close to  
25 the nose.

Compositions adopted for nasal administration which use liquid carriers include nasal sprays or nasal drops. These may comprise aqueous or oil solutions of the active ingredient.



Pharmaceutical compositions adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of apparatus, e.g. pressurised aerosols, nebulizers or insufflators. Such apparatus  
5 can be constructed so as to provide predetermined dosages of the active ingredient.

*(vi) Vaginal Administration*

Pharmaceutical compositions adapted for vaginal administration may be provided  
10 as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

*(vii) Parenteral Administration*

Pharmaceutical compositions adapted for parenteral administrations include aqueous and non-aqueous sterile injectable solutions or suspensions. These may  
15 contain antioxidants, buffers, bacteriostats and solutes which render the compositions substantially isotonic with the blood of an intended recipient. Other components which may be present in such compositions include water, alcohols, polyols, glycerine and vegetable oils, for example. Compositions adapted for parenteral administration may be presented in unit-dose or multi-dose containers,  
20 for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of a sterile liquid carrier, e.g. sterile water form injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

25

Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

In a final aspect the present invention provides a method for enhancing the T cell

immune response which comprises administering to a subject an effective amount of an IFN- $\alpha$  subtype.

The invention will now be described by reference to the following example which  
5 should not be construed as in any way limiting the scope of the invention.

The examples refer to the figures in which:

10 **FIGURE 1:** shows inhibition of peripheral blood T cell proliferation in response to IL-2 and anti-CD3; and

**FIGURE 2:** shows the effect of various IFN $\alpha$  subtypes on the production of IFN $\gamma$  by T cells in the presence or absence of anti-CD3 antibodies plus IL-2.

15

#### EXAMPLE 1

Peripheral blood T cells were purified by Ficoll density gradient centrifugation and E rosetting with sheep red blood cells (SRBC) to separate B and T cells. The T cells were recovered from the rosettes by lysis of the SRBC and were cultured at  
20  $1 \times 10^6$  cells/ml in RPMI 1640 medium with 10% FCS and gentamycin for three days.

$^3\text{H}$  thymidine was added for the last 8 hours culture and incorporation was measured by scintillation counting. The cells were stimulated with anti-CD3  
25 (UCHT1) at  $2 \mu\text{g/ml}$ . Under these conditions none of the IFN- $\alpha$  subtypes induced significant proliferation of the cells (data not shown).

However, when the T cells were stimulated with anti-CD3 and IL-2, inhibition of the IL-2 induced proliferation could be seen (see figure 1). IFN- $\alpha_3$  was the most

effective, with the other subtypes inhibiting to a lesser extent with the exception of IFN- $\alpha^1$  which was inactive in the assay.

#### EXAMPLE 2

- 5 Peripheral blood T cells were purified as in example 1. To investigate stimulation the cells were exposed to IFN $\alpha$  subtypes in the presence or absence of anti-CD3 antibodies (UCHT-1) plus IL-2 and IFN $\gamma$  production was measured using standard intracellular staining techniques. The results are shown in figure 2 and indicate that anti-CD3 plus IL-2 antibodies plus IFN $\alpha_8$  caused an increase in the proportion of
- 10 cells producing IFN $\gamma$ .

CLAIMS:

1. The use of an IFN- $\alpha$  subtype in the preparation of a medicament to enhance the T cell immune response.  
5
2. The use of an IFN- $\alpha$  subtype in the preparation of a medicament for the treatment of cancer.
3. The use of an IFN- $\alpha$  subtype in the preparation of a medicament for the  
10 treatment of a bacterial or parasitic infection.
4. The use of an IFN- $\alpha$  subtype in the preparation of a medicament to treat a systemic viral infection.
- 15 5. The use as claimed in any one of claims 1 to 4 wherein the subtype is IFN- $\alpha_3$ .
6. A pharmaceutical formulation for use in enhancing the T cell immune response which comprises an IFN- $\alpha$  subtype, optionally together with one or more pharmaceutically acceptable carriers, excipients or diluents.  
20
7. A pharmaceutical formulation for use in the treatment of cancer which comprises an IFN- $\alpha$  subtype, optionally together with one or more pharmaceutically acceptable carriers, excipients or diluents.
- 25 8. A pharmaceutical formulation for use in the treatment of bacterial or parasitic infections which comprises an IFN- $\alpha$  subtype, optionally together with one or more pharmaceutically acceptable carriers, excipients or diluents.
9. A pharmaceutical formulation for use in the treatment of systemic viral

infections which comprises an IFN- $\alpha$  subtype, optionally together with one or more pharmaceutically acceptable carriers, excipients or diluents.

10. A pharmaceutical formulation as claimed in any one of claims 6 to 9 wherein  
5 the subtype is IFN- $\alpha_8$ .

11. A method of enhancing a subject's T cell immune response which comprises administering an effective amount of an IFN- $\alpha$  subtype to the subject.

10 12. A method for the treatment of cancer which comprises administering an effective amount of an IFN- $\alpha$  subtype to the subject.

13. A method for the treatment of a bacterial or parasitic infection which comprises administering an effective amount of an IFN- $\alpha$  subtype to the subject.

15

14. A method for the treatment of a systemic viral infection which comprises administering an effective amount of an IFN- $\alpha$  subtype to the subject.

15. A method as claimed in any one of claims 11 to 14 wherein the subtype is  
20 IFN- $\alpha_8$ .

1/2

INHIBITION OF PERIPHERAL BLOOD T CELL PROLIFERATION IN  
RESPONSE TO IL-2 AND ANTI-CD3.

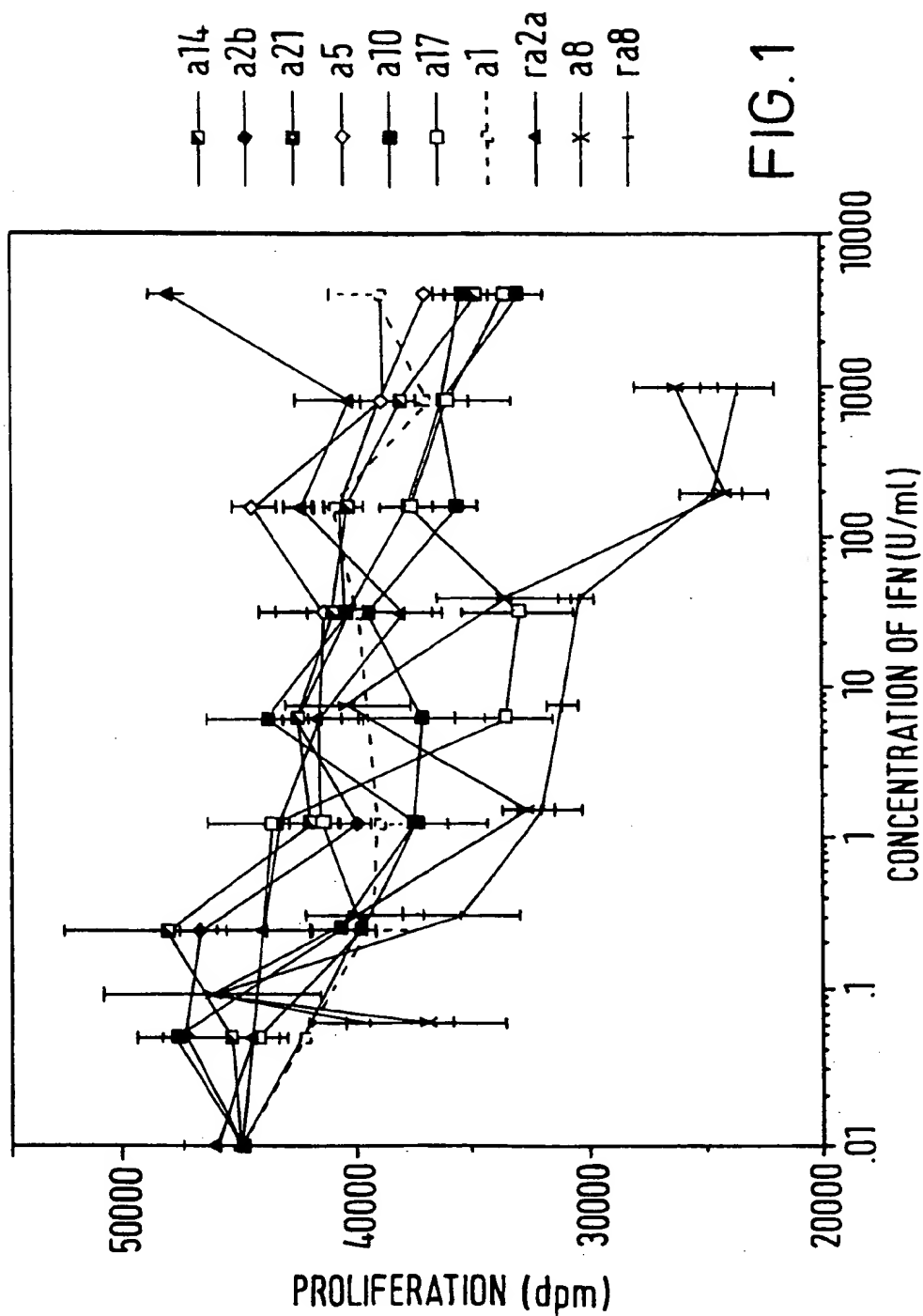
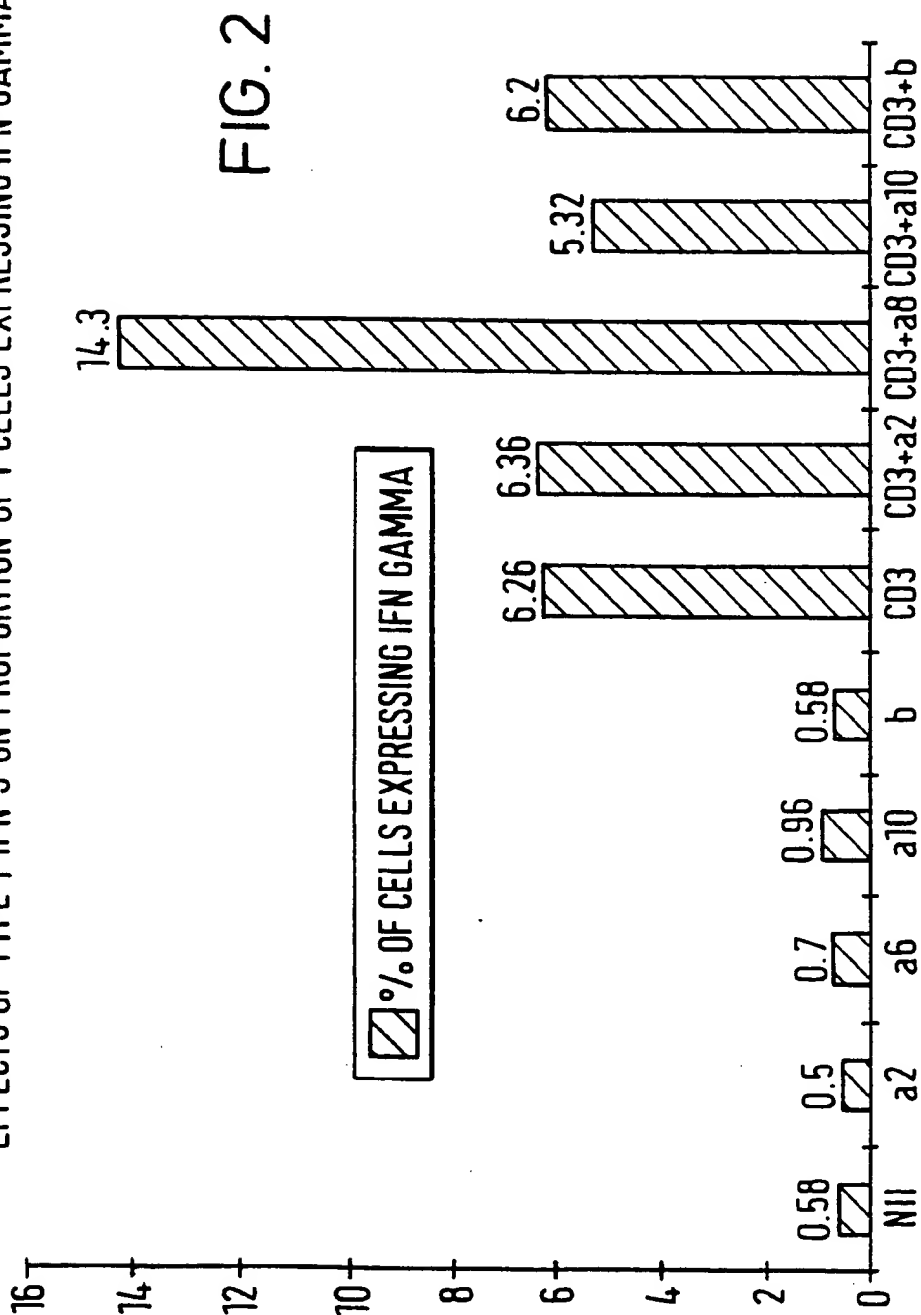


FIG. 1

2/2

EFFECTS OF TYPE 1 IFN'S ON PROPORTION OF T CELLS EXPRESSING IFN GAMMA



# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/00269

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K38/21

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 24212 A (IMPERIAL COLLEGE OF SCIENCE, TECHNOLOGY & MEDICINE) 14 September 1995 cited in the application see the whole document ---	1-15
Y	WO 94 14474 A (SCHERING CORPORATION) 7 July 1994 see the whole document ---	1-15
A	WO 94 20122 A (GEORGETOWN UNIVERSITY) 15 September 1994 see the whole document ---	1-15
-/-		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

11 May 1998

Date of mailing of the international search report

29. 05. 1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Moreau, J



# INTERNATIONAL SEARCH REPORT

Internat/	Application No
PCT/GB	98/00269

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>FOSTER G R ET AL: "Different relative activities of human cell-derived interferon -alpha subtypes: IFN-alpha has very high antiviral potency."  JOURNAL OF INTERFERON AND CYTOKINE RESEARCH 16 (12). 1996. 1027-1033,  XP002064516  see the whole document</p>	1-15
P,X	<p style="text-align: center;">---</p> <p>HIBBERT L M ET AL: "Activity of different interferon alpha subtypes: alpha-8 is the most potent anti-viral subtype and has unique immunomodulatory properties."  32ND ANNUAL MEETING OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF LIVER, LONDON, ENGLAND, UK, APRIL 9-12, 1997.  JOURNAL OF HEPATOLOGY 26 (SUPPL. 1). 1997. 186, XP002064517  see the whole document</p> <p style="text-align: center;">-----</p>	1-15

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB 98/00269

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 11-15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No  
PCT/GB 98/00269

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9524212 A	14-09-1995	AU 1854695 A EP 0741577 A JP 9509955 T	25-09-1995 13-11-1996 07-10-1997
WO 9414474 A	07-07-1994	AU 5953494 A MX 9307733 A	19-07-1994 30-06-1994
WO 9420122 A	15-09-1994	AU 6354994 A	26-09-1994